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## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(54) Title: SYNERGISTIC COMBINATION OF A SUBSTANCE WITH GASTRIC ACID SECRETION INHIBITING EFFECT AND AN ACID DEGRADABLE ANTIBIOTIC

(57) Abstract

The invention consists of a combination of a substance that increases the intragastric pH and an acid degradable antibacterial compound. By this combined product regimen it will be possible to obtain maximal local antibacterial effect of acid degradable antibiotics as well as enhanced bioavailability of the active antibiotic, thus resulting in higher amounts of the active compound in the gastric mucosa due to secretion of weak bases. Both pharmacological effects contribute to drastically increased antimicrobial capacity of acid degradable antibiotics to be used against local infections in the gastrointestinal tract causing gastritis and/or peptic ulcer. The invention also relates to the use of said combination and a process for the preparation thereof.

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5 SYNERGISTIC COMBINATION OF A SUBSTANCE WITH GASTRIC ACID  
SECRETION INHIBITING EFFECT AND AN ACID DEGRADABLE  
ANTIBIOTIC

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10 Field of the Invention

The present invention relates to a combination of a substance with inhibiting effect on the gastric acid secretion, thus a substance which increases the intragastric pH e.g. proton pump inhibitors, histamin-H<sub>2</sub>-blockers and one or more antibacterial compounds which are acid degradable.

Background of the Invention

20 In the treatment of the peptic ulcer disease current therapy aims at reducing the gastric acid secretion, thus resulting in a recess of the injuries in the gastrointestinal tract. Inhibitors of the gastric acid secretion, proton pump inhibitors in particular, induce a rapid relief of pain and other symptoms associated with the ulcer disease. However, relapses of the disease is a documented fact. Since gastric antisecretory therapy only leads to reduction of the major tissue irritating factor, 25 gastric acid, the plausible cause of the disease, *Helicobacter pylori*, remains mainly unaffected. ( *Helicobacter pylori* was earlier named *Campylobacter pylori*.)

30 35 *Helicobacter pylori* is affected by certain antibiotic compounds e.g. macrolides and penicillins as has been shown in vitro and in vivo. However, these products are degraded into nonantibacterial metabolites in the

presence of gastric acid, which drastically reduces their antibacterial efficacy.

In view of the widespread use of antimicrobial pharmaceuticals in the treatment of infectious diseases or for other purposes and the consequent emergence of drug-resistant strains, increased incidence of microbial substitution due to disturbance of the normal bacterial flora, changes in profile of infectious diseases, etc., there has been a constant demand for the development of new antimicrobial agents or combinations thereof.

Prior art

15

Proton inhibitors e.g. omeprazole and its pharmaceutically acceptable salts, which are used in accordance with the invention, are known compounds, e.g. from EP 5129 and EP 124495 and can be produced by known processes. From US 5093342 it is also known that omeprazole can be used in the treatment of Helicobacter infections. Further it has earlier been proposed in WO 92/04898 to use a specific antibiotic, amoxycillin, which is stable in gastric acid, in combination with omeprazole in the treatment of duodenal ulcers. No specific test data are included in said document.

From e.g. Science, March 22, 1946, p. 359-361 it is known that if acid degradable penicillins are administered orally they will be destroyed by the acid content in the stomach.

Further it is described in Eur. J. Clin. Microbiol. Infect. Dis., August 1988, p. 566-569 that some acid degradable antibiotics are active in vitro against *Helicobacter pylori*.

Outline of the invention.

It has now unexpectedly been found that a combination of a substance with inhibiting effect on the gastric acid secretion, thus a substance which increases the intragastric pH e.g. proton pump inhibitors, histamin-H<sub>2</sub>-blockers and one or more antibacterial compounds which is acid degradable give high plasma concentration of the antibiotic following oral administration.

By reducing the acidity in the stomach it is possible to markedly increase the bioavailability of acid-degradable antibiotics thus leaving more of a given dose of the compound available for local antibacterial effect as well as for absorption. Selection of narrow-spectrum antibiotics e.g. benzylpenicillin is favourable since such antibiotics have few side-effects. Due to known physico-chemical properties in general of weak bases like for instance omeprazole, the selection of weak bases e.g. erythromycin favours an increased accumulation of the antibiotic in the stomach wall and gastric crypts where the microbs e.g. Helicobacter pylori resides.

Thus, by combining the components of the present invention synergism of the antibacterial effect of antibiotic compounds is achieved resulting in an improved therapeutic efficacy.

The new combination is especially directed to the treatment of gastropathies e.g. induced by Helicobacter pylori infections. Helicobacter pylori is a gram-negative spirilliform bacterium which colonises in the gastric mucosa. Treatment with commonly used acid degradable antibiotics alone has given insufficient effect.

35

The combination of 5-methoxy-2-[(4-methoxy-3,5-dimethyl-

2-pyridinyl)methyl]sulfinyl}-1H-benzimidazole (generic name: omeprazole) or pharmaceutically acceptable salts thereof and an acid degradable antibiotic give an especially high plasma concentration of the antibiotic following oral administration.

The salt of omeprazole according to the invention is an alkaline pharmaceutically acceptable salt. Examples of such salts include inorganic salts, such as alkali metal salts, e.g. sodium salt, potassium salt etc., alkaline earth metal salts, e.g. calcium salt, magnesium salt etc., ammonium salt, organic salts such as organic amine salts, e.g. trimethylamine salt, triethylamine salt, pyridine salt, procaine acid, picoline salt, dicyclohexylamine salt, N,N-dibenzylethylenediamine salt, N-methylglucamine salt, diethanolamine salt, triethanolamine salt, tris(hydroxymethylamino)methane salt, phenylethylbenzylamine salt, dibenzylethylenediamine salt.

Also other proton pump inhibitors, such as lansoprazole may be used according to the invention. The antibiotic used in the combination should be of the kind, which has a bioavailability which may be improved due to elevation of intragastric pH. It should also be an antimicrobial compound with a very narrow spectrum e.g. benzylpenicillin.

Other examples are acid degradable and acid semi-stable macrolides e.g. erythromycin base and clarithromycin (Nakagawa et al., Chem. Pharm. Bull., 1992, 40, 725-28). Further examples are antibiotics and/or salts thereof which are pharmaceutically engineered for acid protection like for instance enteric coating (e.g. Ery-Max®).

The antibacterial activity against Helicobacter pylori as

indicated by MIC-values of macrolides is drastically decreased with increased pH of the medium in vitro (Melanoski et al., ICAAC, 1992, abstract 713, p 229).

5 The combination according to the present invention can be produced in one pharmaceutical formulation comprising both active ingredients or in two separate tablets or capsules, powder, mixture, effervescence tablets or solution.

10 The active ingredients according to the invention are administered in the form of a pharmaceutical preparation containing the active ingredients as such (e.g. the free base in the case of erythromycin) or in the case of omeprazole also as a salt thereof in combination with a pharmaceutically acceptable carrier by the oral or parenteral route. The carrier mentioned above may be a solid, semi-solid or liquid diluent or a capsule.

15 Compatible dosage forms include various types of tablets, capsules, granules, powders, oral liquids, injections and so on. The proportions of the active ingredient in the total composition is generally 0.1 to 100 weight percent and preferably 0.1 to 95 weight percent.

20 In the manufacture of a pharmaceutical preparation for oral administration, the active ingredient can be formulated with a solid particulate carrier such as lactose, sucrose, sorbitol, mannitol, starch, amylopectin, a cellulose derivative or gelatin, and a lubricating agent such as magnesium stearate, calcium stearate or polyethylene glycol wax may be further incorporated. The resulting composition is then compressed into tablets. Coated tablets or dragees can be manufactured by coating the core tablets, thus prepared, 25 with a thick sugar solution containing gum arabic, gelatin, talc, titanium dioxide, etc. or a lacquer

prepared using a volatile organic solvent or solvent mixture.

Soft gelatin capsules can be manufactured by filling a  
5 composition comprising the active ingredient and a known vegetable oil into capsules. Hard gelatin capsules can be manufactured by filling into capsules the granules or pellets each comprising the active ingredient and a solid particulate carrier such as lactose, sucrose, sorbitol,  
10 mannitol, potato starch, corn starch, amylopectin, a cellulose derivative or gelatin.

The dosage of omeprazole or a salt thereof and the antibiotic depends on individual needs (for example, the patient's condition, body weight, age, sex, etc.) as well as on the method of administration. Generally speaking, the oral dosage may range from 1 to 200 mg of omeprazole per day and up to 10 g of acid degradable antibiotic per adult human. Each may be administered in one to a few  
20 divided doses.

#### Pharmacological tests

25 Benzylpenicillin was administered alone to eight healthy volunteers and in combination with omeprazole and the plasma concentration was measured. When benzylpenicillin was administered alone the plasma concentrations were insufficient for a therapeutical effect (Table 1). When benzylpenicillin was combined with omeprazole therapeutic useful plasma concentrations were reached  
30 (Table 2). Similar results were obtained after oral administration of erythromycin lactobionate prior and after omeprazole induced reduction of acid secretion in man (Tables 3 and 4). Semidegradable macrolides, e.g.  
35 Ery-Max® and clarithromycin are absorbed to a certain

extent (Tables 5 and 7). However, after administration of an acid secretion inhibitor, omeprazole, a marked increase of the bioavailability of the macrolides is shown as indicated by the difference in  $C_{max}$  and AUC in 5 healthy volunteers (Tables 6 and 8). Compare also Fig. 1 and Fig. 2 showing the accurate plasma concentrations of Ery-Max® and clarithromycin with and without omeprazole. The high plasma concentrations of the antibiotics after reduction of the gastric acid secretion is evidence for a great reduction of the degradation in the stomach of the 10 antibiotics used. This results in an increased amount of the active antibiotic in the gastric lumen, thus resulting in increased local antimicrobial effect. It also leads to a larger amount of the antibiotic available 15 for absorption, thus resulting in increased plasma and tissue levels of the antibiotic (increased bioavailability). The best mode of carrying out the invention at present is to combine omeprazole with erythromycin.

Concentration in plasma of benzylpenicillin after oral administration Dose 1.0 g.

Table 1  
(without omeprazole)

Person number	Plasma concentration mg/L						Cmax mg/L	AUC H·mg /L
	15'	30'	45'	1 h	1.5 h	2 h		
1	0.24	0.50	0.54	0.41	0.22	0.135	0.074	<0.02
2	0.53	1.60	1.47	1.24	0.52	0.30	0.14	<0.02
3	0.23	0.51	0.45	0.37	0.21	0.11	0.051	<0.02
4	0.076	0.23	0.20	0.15	0.084	0.053	0.044	<0.02
5	0.26	0.50	0.41	0.40	0.28	0.17	0.071	0.042
6	0.33	0.37	0.26	0.20	0.099	0.051	0.038	<0.02
7	0.17	0.26	0.23	0.17	0.14	0.075	0.027	<0.02
8	0.104	0.125	0.124	0.121	0.062	0.050	0.021	<0.02
Mean	0.24	0.51	0.46	0.38	0.20	0.118	0.058	<0.02
value								
± S.D.								

Cmax:tdep=4.163 P<0.01

AUC:tdep=5.553 P<0.001

Concentration in plasma of benzylpenicillin after oral administration Dose 1.0 g.  
 Table 2 (with omeprazole)

Person number	Plasma concentration mg/L						Cmax mg/L	AUC H·mg/L
	15'	30'	45'	1 h	1.5 h	2 h		
1	0.89	2.98	3.25	3.41	3.74	2.79	0.89	0.70
2	0.73	2.80	5.51	5.74	2.26	1.62	0.84	0.76
3	1.40	6.24	9.85	9.75	6.59	1.67	0.53	0.30
4	0.11	0.72	1.22	3.05	7.57	5.59	2.94	0.45
5	0.64	2.48	2.45	2.10	1.95	1.10	0.46	0.25
6	1.24	3.22	3.65	3.57	1.42	0.84	0.55	0.33
7	0.33	0.83	1.43	1.52	1.17	0.87	0.45	0.21
8	0.62	1.37	2.31	2.35	2.54	1.37	0.48	0.23
Mean value	0.745	2.58	3.71	3.94	3.41	1.98	0.89	0.40
± S.D.								

Cmax:tdep=4.163 P<0.01  
 AUC:tdep=5.553 P<0.001

Concentration in plasma of erythromycin lactobionate after oral administration. Dose: 1.0 g.

Table 3 1(2) Without preceding omeprazole treatment

Subject number	Serum levels in mg/L at indicated times									
	0	15'	30'	45'	1 h	1.5 h	2 h	3 h	4 h	6 h
1	<0.015	0.015	0.15	0.29	0.28	0.20	0.18	0.13	0.091	0.047
2	<0.015	0.26	0.33	0.30	0.25	0.25	0.18	0.15	0.16	0.070
3	<0.015	0.042	0.22	0.21	0.24	0.14	0.13	0.12	0.86	0.049
4	<0.015	0.032	0.042	0.030	0.039	0.078	0.084	0.076	0.072	0.046
5	<0.015	0.023	0.13	0.16	0.16	0.15	0.14	0.12	0.082	0.051
6	<0.015	0.068	0.12	0.094	0.11	0.098	0.077	0.074	0.059	0.034
7	<0.015	0.57	0.98	0.75	0.68	0.43	0.37	0.32	0.27	0.088
8	<0.015	0.071	0.27	0.33	0.23	0.16	0.16	0.12	0.095	0.044
Mean value	<0.015	0.135	0.28	0.27	0.25	0.18	0.165	0.14	0.11	0.054
± S.D.		±0.193	±0.30	±0.22	±0.19	±0.11	±0.092	±0.078	±0.070	±0.017

Concentration in plasma of erythromycin lactobionate after oral administration. Dose 1.0 g.

Table 3 2(2) With preceding omeprazole treatment

Table 4

Kinetic data following oral administration(s) of erythromycin lactobionate to 8 healthy volunteers with and without co-administration of omeprazole. A cross over study.

Omeprazole	$C_{max}$ mg/L mean $\pm$ SD	$T_{max}$ h median	AUC H.mg/L 0-6 H
YES	8.38 $\pm$ 0.28	0.5	21.74 $\pm$ 8.64
NO	0.32 $\pm$ 0.28	0.75	0.83 $\pm$ 0.55

Blood serum levels of erythromycin Ery-Max® following oral administration. Dose 500 mg.

Table 5 1(2) Without preceeding omeprazole treatment.

Subject number	Serum levels in mg/L at indicated times (min)						
	0	30 m	60 m	90 m	120 m	150 m	180 m
1	0.00	0.06	0.06	0.06	0.12	0.28	1.90
2	0.00	0.06	0.06	0.06	0.06	0.06	0.65
3	0.00	0.06	0.06	0.06	0.06	0.08	0.75
4	0.00	0.06	0.06	0.06	0.06	0.16	0.43
5	0.00	0.06	0.06	0.06	0.06	0.25	0.95
6	0.00	0.06	0.06	0.06	0.06	0.06	1.50
7	0.00	0.06	0.06	0.06	0.41	0.68	1.10
8	0.00	0.06	0.06	0.10	0.38	0.51	1.20
Mean	0.00	0.06	0.07	0.10	0.17	0.35	0.87
Sdev	0.00	0.00	0.01	0.11	0.18	0.40	0.69
							0.34
							0.10
							0.01

Blood serum levels of erythromycin Ery-Max® following oral administration. Dose 500 mg.

Table 5 2(2) Without preceding omeprazole treatment.

Subject number	AUC levels at indicated times (min)								Tot AUC			
	30 m	60 m	90 m	120 m	150 m	180 m	300 m	480 m				
0	0.015	0.03	0.03	0.045	0.1	0.545	2.66	1.365	0.42	5.21		
1	0	0.015	0.03	0.03	0.03	0.03	0.71	1.26	0.5	2.635		
2	0	0.015	0.03	0.03	0.03	0.036	0.208	1.24	1.035	0.52	3.144	
3	0	0.015	0.03	0.03	0.03	0.055	0.148	1.35	1.755	0.646	4.059	
4	0	0.015	0.03	0.03	0.03	0.078	0.3	2.45	2.925	1.036	6.894	
5	0	0.015	0.03	0.03	0.03	0.03	0.03	0.58	1.035	0.46	2.24	
6	0	0.015	0.03	0.03	0.03	0.03	0.03	0.99	0.52	4.16		
7	0	0.015	0.04	0.12	0.198	0.273	0.445	1.56	2.56	1.755	0.74	6.425
8	0	0.015	0.03	0.03	0.143	0.428	0.725	1.639	1.515	0.605		
Mean	0	0.015	0.031	0.041	0.067	0.129	0.304	0.827	0.647	0.202		
Sdev	0	0.015	0.004	0.032	0.066	0.145	0.25					

AUC: 4.34 ± 1.7

C<sub>max</sub>: 1.005

Blood serum levels of erythromycin Ery-Max® following oral administration. Dose 250 mg.

Table 6.1 (2) With preceeding omeprazole treatment.

Subject number	Serum levels in mg/L at indicated times (min)						
	0	30 m	60 m	90 m	120 m	150 m	180 m
1	0.00	0.06	0.54	3.2	2.4	2.3	1.9
2	0.00	0.06	0.06	0.1	0.69	2.1	1.7
3	0.00	0.06	0.29	1.2	2.5	2.5	1.4
4	0.00	0.06	0.06	0.094	0.84	0.74	0.37
5	0.00	0.06	0.06	0.059	0.58	1.5	1.7
6	0.00	0.06	0.068	0.49	1.2	0.86	0.68
7	0.00	0.06	0.057	1.1	1.3	2	2.1
8	0.00	0.06	0.48	1.4	1.9	1.6	1.7
Mean	0.00	0.06	0.20	0.96	1.43	1.7	1.44
Sdev	0.00	0.00	0.21	1.06	0.76	0.65	0.61
						0.38	0.13
							0.01

Blood serum levels of erythromycin Ery-Max® following oral administration. Dose 250 mg.

Table 6 2 (2) with precedingomeprazole treatment.

Subject number	AUC levels at indicated times (min)								Tot AUC
	0	30 m	60 m	90 m	120 m	150 m	180 m	300 m	
1	0.015	0.15	0.935	1.4	1.175	1.05	2.69	1.515	0.56
2	0.00	0.015	0.03	0.04	0.198	0.698	0.95	2.24	1.02
3	0.00	0.015	0.088	0.373	0.925	1.25	0.975	2.15	1.47
4	0.00	0.015	0.03	0.039	0.234	0.395	0.278	1.67	2.625
5	0.00	0.015	0.03	0.03	0.16	0.52	0.8	3.3	3.15
6	0.00	0.015	0.032	0.14	0.423	0.515	0.385	1.16	0.93
7	0.00	0.015	0.029	0.289	0.6	0.825	1.025	2.97	1.71
8	0.00	0.015	0.0135	0.47	0.825	0.875	0.825	2.7	1.92
Mean	0.00	0.015	0.065	0.289	0.595	0.782	0.786	2.36	1.793
Sdev	0.00	0.00	0.052	0.31	0.434	0.312	0.295	0.703	0.764
									0.702
									0.284

AUC: 7.38 ± 1.9

Cmax: 1.94

Blood serum levels of clarithromycin following oral administration. Dose 250 mg.

Table 7 1(2) Without proceeding omeprazole treatment

Subject number	Serum levels in mg/L at indicated times (min)									
	0	30 m	60 m	90 m	120 m	150 m	180 m	360 m	660 m	840 m
1	0.00	0.11	0.97	0.92	1.1	1.5	1.2	0.96	0.41	0.26
2	0.00	0.12	0.15	0.24	0.28	0.36	0.47	0.53	0.18	0.14
3	0.00	0.06	0.11	0.092	0.11	0.12	0.17	0.55	0.2	0.12
4	0.00	0.06	0.06	0.044	0.099	0.13	0.15	0.48	0.23	0.13
5	0.00	0.06	0.06	0.062	0.064	0.13	0.18	0.54	0.2	0.16
6	0.00	0.07	0.13	0.2	0.3	0.37	0.45	0.23	0.14	0.082
7	0.00	0.12	0.26	0.27	0.46	0.81	0.78	0.64	0.2	0.12
8	0.00	0.06	0.31	0.38	0.41	0.55	0.57	0.64	0.27	0.16
Mean	0.00	0.08	0.26	0.28	0.35	0.50	0.50	0.57	0.23	0.15
Sdev	0.00	0.03	0.30	0.28	0.34	0.47	0.36	0.20	0.08	0.05

Blood serum levels of clarithromycin following oral administration. Dose 250 mg.

Table 7.2(2) Without preceding omeprazole treatment.

Subject number	0	AUC levels at indicated times (min)								TOT AUC
		30 m	60 m	90 m	120 m	150 m	180 m	360 m	660 m	
1	0.00	0.028	0.27	0.473	0.505	0.65	0.675	2.16	4.11	1.005
2	0.00	0.03	0.068	0.098	0.13	0.16	0.208	1	2.13	0.48
3	0.00	0.015	0.043	0.051	0.051	0.058	0.073	0.72	2.25	0.48
4	0.00	0.015	0.03	0.026	0.036	0.057	0.07	0.63	2.13	0.54
5	0.00	0.015	0.03	0.031	0.032	0.049	0.078	0.72	2.22	0.54
6	0.00	0.018	0.05	0.083	0.125	0.168	0.205	0.68	1.11	0.333
7	0.00	0.03	0.095	0.133	0.183	0.318	0.398	1.42	2.52	0.48
8	0.00	0.015	0.093	0.173	0.198	0.24	0.28	1.21	2.73	0.645
Mean	0.00	0.021	0.085	0.133	0.157	0.212	0.248	1.068	2.4	0.563
Sdev	0.00	0.007	0.079	0.146	0.154	0.201	0.207	0.525	0.838	0.199

AUC: 4.88 ± 2.24

C<sub>max</sub>: 0.68

Blood serum levels of clarithromycin following oral administration. Dose 250 mg.

Table 8.1(2) With preceding omeprazole treatment.

Subject number	Serum levels in mg/L at indicated times (min)									
	0	30 m	60 m	90 m	120 m	150 m	180 m	360 m	660 m	840 m
1	0.00	1.9	2.3	2.2	1.7	1.7	1.7	0.86	0.37	0.28
2	0.00	0.078	3	1.9	1.9	1.9	1.7	0.78	0.34	0.16
3	0.00	0.6	1.6	1.3	1.1	1.1	1.05	0.68	0.23	0.14
4	0.00	0.06	1.2	1.3	1.2	1.03	1.1	0.68	0.39	0.2
5	0.00	0.096	2.1	1.6	1.3	1.1	1.1	0.77	0.27	0.18
6	0.00	0.21	1.2	1.8	1.6	1	1.5	0.67	0.22	0.13
7	0.00	0.12	0.99	1.1	0.9	0.89	1.07	0.61	0.22	0.16
8	0.00	1.07	2.2	2	2	1.7	1.8	0.92	0.38	0.24
Mean	0.00	0.52	1.82	1.65	1.46	1.30	1.38	0.75	0.30	0.19
Sdev	0.00	0.66	0.69	0.39	0.40	0.39	0.33	0.11	0.08	0.05

Blood serum levels of clarithromycin following oral administration. Dose 250 mg.

Table 8 2(2) With preceding omeprazole treatment.

Subject number	AUC levels at indicated times (min)										Tot AUC
	0	30 m	60 m	90 m	120 m	150 m	180 m	360 m	660 m	840 m	
1	0.00	0.475	1.05	1.125	0.975	0.85	0.85	2.56	3.69	0.975	12.55
2	0.00	0.02	0.77	1.225	0.95	0.95	0.9	2.48	3.36	0.75	11.4
3	0.00	0.15	0.55	0.725	0.6	0.55	0.538	1.73	2.73	0.555	8.128
4	0.00	0.015	0.315	0.625	0.625	0.558	0.533	1.78	3.21	0.885	8.545
5	0.00	0.024	0.549	0.925	0.725	0.6	0.55	1.87	3.12	0.675	9.038
6	0.00	0.053	0.353	0.75	0.85	0.65	0.625	2.17	2.67	0.525	8.545
7	0.00	0.03	0.278	0.523	0.5	0.448	0.49	1.68	2.49	0.57	7.008
8	0.00	0.268	0.818	1.05	1	0.925	0.875	2.72	3.9	0.93	12.49
Mean	0.00	0.129	0.585	0.868	0.778	0.691	0.67	2.124	3.146	0.733	
Sdev	0.00	0.165	0.275	0.251	0.192	0.191	0.174	0.416	0.499	0.18	

AUC: 9.7 ± 2.1

C<sub>max</sub>: 1.9

### Discussion

The advantage of the present combination of a compound that increases the intragastric pH, such as omeprazole and an acid degradable antibiotic, is that the bioavailability of the antibiotic will increase resulting in sufficient plasma levels for therapeutic effects. Another advantage is that there will be increased amounts of the acid degradable antibiotic in the gastric lumen.

Benzylpenicillin is interesting because it has a very narrow spectrum and therefore exerts a very limited effect on the normal intestinal flora.

By reducing the gastric acid secretion or acid neutralisation in the stomach the pH increases. Due to the less acidic milieu the orally administered acid degradable antibiotic will be less catabolized and thus locally exerting its antimicrobial effect. Another advantage is that increased amounts of the antibiotic will pass into the small intestine where it will be absorbed in biologically active form. Increasing the intragastric pH is also favourable for antibiotic efficacy as shown in vitro. If the pH of the medium where *Helicobacter pylori* is grown in vitro is reduced varying degrees below pH 7 the antibacterial properties rapidly decrease.

Those antibiotics which are weak bases e.g. macrolides will be excreted via the stomach wall due to its physico-chemical properties in congruence with other known weak bases i.e. nicotine, aminopurine and omeprazole (Larsson et al., Scand. J. Gastroenterol., 1985, 900-7). Thus, the antibiotic weak base will be biologically concentrated in the stomach wall, where the bacteria (e.g. *Helicobacter pylori*) reside.

CLAIMS

1. The combination of a substance with inhibiting effect on the gastric acid secretion which increases the intragastric pH and an acid degradable antibacterial compound.
2. The combination according to claim 1 wherein the substance with inhibiting effect on the gastric acid is a proton pump inhibitor.
3. The combination according to claim 2 wherein the proton pump inhibitor is 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl-1H-benzimidazole or a pharmaceutically acceptable salt thereof.
4. The combination according to claim 1 with effect on gastritis and peptic ulcer caused by microbes.
5. The combination according to claim 1 with effect on gastritis and peptic ulcer caused by Helicobacter pylori.
6. The combination according to claim 1 characterized in that the acid degradable antibacterial compound is benzyl-penicillin.
7. The combination according to claim 1 characterized in that the acid degradable antibacterial compound is weak base antibiotics.
8. The combination according to claim 7 characterized in that the weak base antibiotic is erythromycin base.
9. The combination according to claim 7 characterized in that the antibiotic is clarithromycin.
10. Use of the combination according to claim 1 for the manufacture of a medicament for the treatment of gastritis and peptic ulcer caused by Helicobacter pylori.
11. A method for the treatment of gastritis and peptic

ulcer caused by Helicobacter pylori comprising oral administering to a patient suffering therefrom a substance with inhibiting effect on the gastric acid secretion which increases the intragastric pH together with an amount of an acid degradable antibacterial compound sufficient for the treatment of said infection.

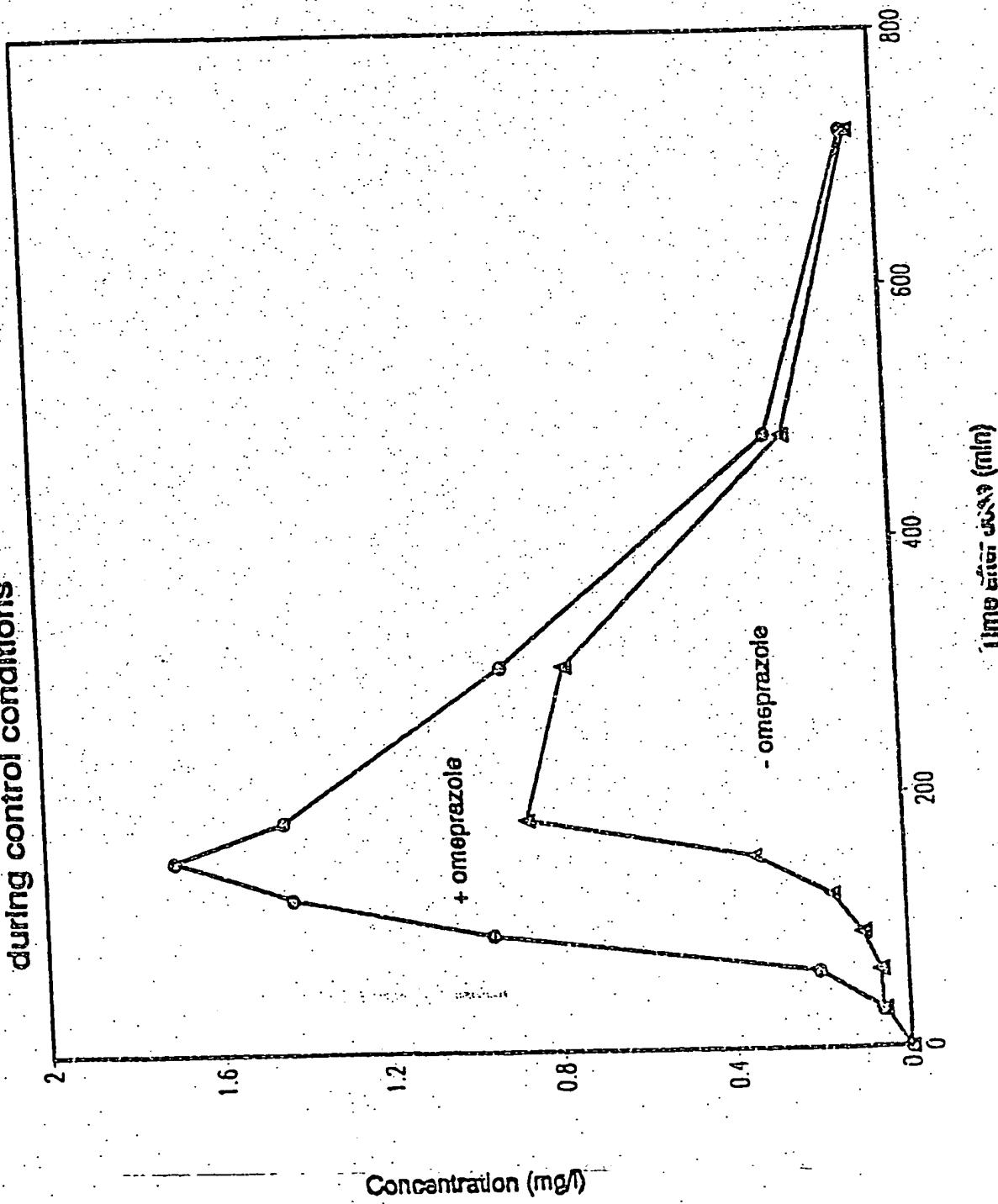
12. A pharmaceutical preparation for use in the treatment of gastritis and peptic ulcer caused by Helicobacter pylori infections wherein the active ingredients are a substance with inhibiting effect on the gastric acid secretion which increases the intragastric pH and an acid degradable antibacterial compound.

13. A process for the preparation of a combination according to claim 1 whereby a substance with inhibiting effect on the gastric acid secretion, which increases the intragastric pH is incorporated into the same preparation as an acid degradable antibacterial compound.

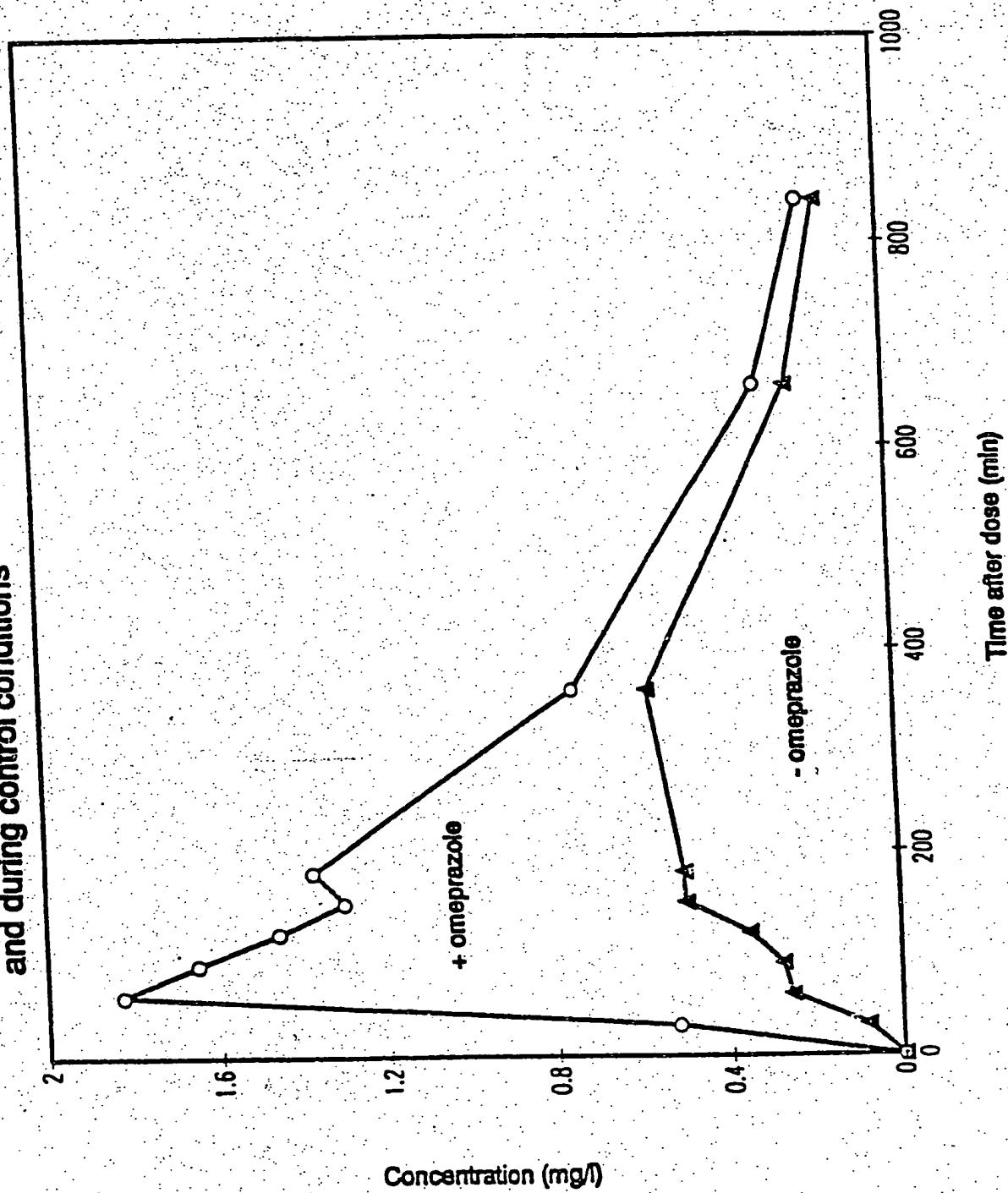
Blood serum levels of erythromycin Ery-Max® in healthy subjects during omeprazole treatment and during control conditions

Fig. 1

1/2



Blood serum levels of clarithromycin in healthy subjects during omeprazole treatment and during control conditions



## INTERNATIONAL SEARCH REPORT

International application N  
PCT/SE 93/00327

## A. CLASSIFICATION OF SUBJECT MATTER

IPC5: A61K 31/44, A61K 31/71  
According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC5: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE, DK, FI, NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EMBASE, MEDLINE, CA, WPI, WPIL, CLAIMS

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	THE LANCET, Volume 340, July 1992, R.P.H. LOGAN et al., "Clarithromycin and omeprazole for Helicobacter pylori" page 239 --	1-5, 7, 8, 9-10, 12-13
X	CURRENT SCIENCE, Volume 8, 1992, C. Stewart Goodwin et al., "Peptic ulcer disease and Helicobacter pylori infection" page 122 - page 127 --	1-5, 8, 10, 12-13
Y	WO, A1, 9204898 (BYK GULDEN LOMBERG), 2 April 1992 (02.04.92), page 4, line 28 - page 5, line 8, claim 7 --	1-8, 10, 12-13

 Further documents are listed in the continuation of Box C. See patent family annex.

- \* Special categories of cited documents:
- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- "&" document member of the same patent family

Date of the actual completion of the international search

Date of mailing of the international search report

10-08-1993

6 August 1993

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## INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 93/00327

## C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO, A1, 9009175 (AKTIEBOLAGET HÄSSLE), 23 August 1990 (23.08.90)	1-8,10,12-13
P,A	Dialog Information Service, file 73, EMBASE, Dialog accession no. 8521149, EMBASE no. 92197053, Loo V.G.: "Helicobacter pylori infection in a pediatric population: In vitro susceptibilities to omeprazole and eight antimicrobial agents, ANTIMICROB. AGENTS CHEMOTHER. (USA), 1992, 36/5 (1133-1135)	1-8,10,12-13

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 93/00327

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.: 11 because they relate to subject matter not required to be searched by this Authority, namely:  
Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods (see PCT Rule 39(iv)).
2.  Claims Nos.: because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3.  Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1.  As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3.  As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4.  No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- The additional search fees were accompanied by the applicant's protest.  
 No protest accompanied the payment of additional search fees.

**INTERNATIONAL SEARCH REPORT**

Information on patent family members

International application No.

02/07/93

PCT/SE 93/00327

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A1- 9204898	02/04/92	AU-A- 8445791 EP-A- 0548103	15/04/92 30/06/93
WO-A1- 9009175	23/08/90	AU-B- 626641 AU-A- 5038190 EP-A- 0414847	06/08/92 05/09/90 06/03/91